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Pain and Confusion

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**BODY:**

An article in the Aug. 22/29 issue of the Journal of the American Medical Association (JAMA) suggested that popular arthritis drugs Vioxx and Celebrex may increase the risk of cardiovascular events -- including heart attacks, strokes and chest pain. The news could affect millions of arthritis patients who currently use the drugs.

Approved in 1999, Vioxx and Celebrex generally help relieve pain without the gastrointestinal symptoms -- such as stomach pain, bleeding and stomach ulcers -- sometimes associated with many other non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen (such as Motrin and Advil).

Vioxx and Celebrex, which belong to a class of drugs called COX-2 inhibitors, hold more than 60 percent of the arthritis drug market and last year had combined sales of just over $ 4 billion. Vioxx was the nation's most heavily advertised prescription drug last year, according to IMS Health, a health information company; Celebrex ranked seventh in advertising.

Both Merck, which makes Vioxx, and Pharmacia, which makes Celebrex, dispute the findings reported in JAMA and insist their drugs are safe.

My doctor recently prescribed Vioxx for my arthritis. TV commercials make it look like a wonder drug. Should I ask for something else?

As you were about to guess, the answer is, "it depends" -- partly on your risk for heart problems otherwise, and partly on other factors. The researchers who wrote the JAMA article, heart specialists at the Cleveland Clinic, examined four previously published studies on the drugs to see how many study subjects suffered cardiovascular events, including a blood clot, heart attack or stroke. So this was not research conducted specifically for the purpose of exploring negative effects on the heart, but an examination of data collected for other purposes to see if they provided any information about these drugs and heart problems.

Oh, so I can ignore the studies?

Well, no. To some experts, they suggest reason for concern. One study showed twice as high a rate of cardiovascular events for people taking Vioxx as for those who took naproxen, another pain reliever. However, the absolute incidence was low: 1.3 percent for the Vioxx group versus 0.67 for those taking naproxen. What isn't clear is whether Vioxx increased risk by causing blood platelets to clump together and thereby promoting a clot, or whether naproxen protected some people from heart attacks by keeping platelets from clumping together.

That doesn't sound good. What about the other studies?

A second study compared Celebrex to two other drugs commonly prescribed for arthritis: ibuprofen and diclofenac (Cataflam and Voltaren). Researchers found more heart attacks in the Celebrex group than other groups, according to Eric Topol, the study's lead author and chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, although he said the difference was not statistically significant. However, some patients in this study also took aspirin, which can protect the heart from clots and heart attacks. The other two studies compared Vioxx with other arthritis drugs, and also included some aspirin-takers. Taken together, says Topol, the four trials consistently showed a small excess of cardiac events among the patients taking Vioxx or Celebrex.

Did all this concern about Celebrex and Vioxx and heart problems come out of the blue?

No. Rheumatologist Stephen Ray Mitchell, academic dean of the Georgetown University Medical School, said other published studies have raised concerns about the effect of Vioxx and Celebrex on platelets. And some members of an FDA advisory committee who reviewed Vioxx earlier this year thought the drug's label should include information on the study that compared Vioxx and naproxen and found more cardiovascular events among the Vioxx takers. The FDA has not yet made a final ruling on the proposed label changes.

So is one drug safer than the other?

Vioxx was linked to more heart attacks in these studies, but Celebrex seems to increase the risk as well, according to the researchers. John Klippel, medical director of the Arthritis Foundation, says the study raises concerns about both drugs and that one drug doesn't appear safer than the other when it comes to heart attack risk.

Do the the manufacturers plan any action in response to the new findings?

Pharmacia and Merck may consider the possibility of conducting clinical trials that would look specifically at cardiovascular risk, spokesmen for the companies said. The Arthritis Foundation and the American College of Rheumatology have called on both companies to do just that.

Mary-Fran Faraji, a spokeswoman for Pharmacia, said Pharmacia continually reviews data on the drugs. She said the JAMA article offers no new data and compares two completely different sets of patients -- those taking aspirin against those who were not. She said no evidence of increased cardiovascular risk from Celebrex had been seen in 30,000 patients in Pharmacia-sponsored clinical trials.

Merck spokeswoman Chris Fanelle said similarly that her company's studies of 28,000 patients suggested "there is no increase in the risk of cardiovascular events as a result of treatment with Vioxx."

What should I do in the meantime?

If you take either drug, Klippel of the Arthritis Foundation advises, you may want to talk with your physician about considering a switch. People who should have the conversation soonest, he says, include those in higher cardiac risk groups such as the elderly, diabetics, smokers, people with a history of heart disease or people with high blood pressure.

Why shouldn't I just switch?

Because most alternatives, such as naproxen or ibuprofen, carry a risk of serious stomach disorders such as bleeding and ulcers; patients with a previous history of an ulcer or stomach disorder may be advised to stick with Vioxx or Celebrex, which were developed to solve that problem. Before you meet with your doctor, have a look at the Arthritis Foundation's Drug Guide (www.arthritis.org/conditions/DrugGuide/drug_index.asp) so you can discuss options available to you.

What are the other drugs I'd most likely switch to?

If Celebrex or Vioxx gave you relief, chances are good your doctor will simply try another NSAID, such as aspirin, ibuprofen or nabumetone (Relafen). Klippel noted that while NSAIDs are chemically similar, people respond differently to them, so that if one doesn't work for you, another might. Some doctors prescribe misoprostol (Cytotec), a synthetic prostaglandin, along with NSAIDs to replace stomach-protecting enzymes that NSAIDs wipe out. A fairly new drug, Arthotec, combines diclofenac, an NSAID, and misoprostol in a single pill. A simple pain reliever such as acetaminophen (Tylenol), which doesn't have the gastrointestinal side effects of NSAIDs, may work fine for some patients but for others may not provide sufficient relief.

What if I keep taking Vioxx or Celebrex but add a baby aspirin to the regimen? Would that let me keep taking the drugs but also help protect against a heart attack?

Maybe, says Mitchell, though no studies have been done to prove this would be effective. And even low-dose aspirin raises the risk of stomach disorders. So talk with your doctor.

Is there any way to monitor for a blood clot, so I could keep taking the drug and just get off it if the doctor spots a problem?

Nope. Tests cannot predict clots.

Any other side effects of these drugs I should know about?

Like some other NSAIDs, Celebrex and Vioxx can, in rare cases, cause fluid retention and kidney problems or raise blood pressure. Your doctor should perform periodic blood tests to make sure markers that could indicate a problem aren't elevated.

Are Celebrex and Vioxx really more effective in relieving arthritis pain?

Celebrex and Vioxx's claim to fame is their lowered risk of stomach problems; they're actually no more effective in reducing pain than a host of other NSAIDs.

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